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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/081,617	02/21/2002	Steffen Panzner	101215-81	9573

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EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 07/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/081,617	PANZNER ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-11 and 21-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5-11 and 21-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment dated 5-19-06 is acknowledged.

The claims included in the prosecution are 1-3, 5-11 and 21-59.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-3, 5-11 and 21-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hafez cited above in combination with Huang (5,283,122).

Hafez discloses large unilamellar liposomes containing cholesteryl hemisuccinate (CHEMS) and DODAC. The pH values are from 4 to 6.7. The sizes of the liposomes are either 153 + 34 nm or 274 nm depending upon the ratios of DODAC and CHEMS (abstract, Materials and Methods and Results). What is lacking in Hafez is the inclusion of a neutral lipid such as cholesterol or phosphatidylcholine.

Huang while disclosing pH sensitive liposomes teaches that inclusion of cholesterol decreases the leakage and the less leaky liposomes containing cholesterol will be particularly useful in discharging their contents into the cytoplasm. The contents

include drugs, enzymes, hormones and others. The anionic lipid is phosphatidic acid or oleic or palmitic acid (abstract, col. 5, lines 16-68, col. 6, lines 25-54).

The inclusion of a neutral lipid such as cholesterol in the liposomes of Hafez would have been obvious to one of ordinary skill in the art since such liposomes are less leaky and discharge the contents in the cytoplasm after fusion as taught by Huang. What is also lacking in Hafez is the inclusion of the active agents in the liposomes. However, in the Discussion section (page 1449, col. 1), Hafez suggests the applicability of the liposomes for the delivery of nucleic acids and therefore, it would have been obvious to one of ordinary skill in the art to encapsulate an active agent in the liposomes of Hafez with a reasonable expectation of success. Hafez is also lacking in the teachings of instant sizes between 60 and 130 nm. However, in the absence of showing the criticality, it is deemed obvious to one of ordinary skill in the art to prepare liposomes of desired sizes depending upon the goal by manipulating the sonicating conditions. Furthermore, Hafez also teaches that the liposomal sizes can be varied by varying the ratios of the lipids and the liposomal sizes of 153 with a standard deviation of 34 (153-34 = 119) fall within the sizes claimed in instant claim 22. Although Hafez does not teach instant cationic lipids such as HisChol, it would have been obvious to use art known compounds in the liposomes of Hafez with the expectation of obtaining similar results since the principle is the same.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that the liposomes are fundamentally different from those of Hafez. According to applicant, the liposomes as currently claimed are stable enough

at a low pH that they are capable of being loaded with polyanions such as nucleic acids and are also stable at a neutral pH. These arguments are not persuasive since Hafez teaches that the pH dependent fusion values can bee changed by changing the amounts of the cationic lipid and the anionic lipid, CHEMS (figure 2) and that these liposomes are meant for the delivery of nucleic acids is evident in the discussion section. Furthermore, the secondary reference of Huang teaches the stability of liposomes by the inclusion of neutral lipid such as cholesterol. Applicant argues that Huang provides no instruction on how to make a liposome that is stable both at a low pH and an neutral pH and that Huang teaches specifically how to avoid leakage of liposomal contents during fusion. The examiner disagrees since Huang teaches that cholesterol improves the stability and reduces the leakage of the liposomal content after the formation and during fusion and not just during fusion. That means stability of liposomes at all times including at low and neutral pH is implicit.

3. Claims 1-3, 5-11 and 21-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hafez cited above in combination with Lishko (5,753,263).

Hafez discloses large unilamellar liposomes containing cholesteryl hemisuccinate (CHEMS) and DODAC. The pH values are from 4 to 6.7. The sizes of the liposomes are either 153 + 34 nm or 274 nm depending upon the ratios of DODAC and CHEMS (abstract, Materials and Methods and Results). What is lacking in Hafez is the inclusion of a neutral lipid such as cholesterol or phosphatidylcholine.

Lishko while disclosing pH sensitive liposomes teaches that the pH sensitive liposomes can be formed by combining phosphatidylcholine or cholesterol with one or

more phospholipids to form pH sensitive liposomes. Lishko further teaches that pH sensitive liposomes contain DOPE and Cholesterol hemisuccinate (col. 15, lines 13-38).

To include either phosphatidylcholine or cholesterol in the liposomal compositions of Hafez with a reasonable expectation of success, would have been obvious to one of ordinary skill in the art since Lishko advocates the use of these in pH sensitive liposomes. Although Hafez does not teach instant cationic lipids such as HisChol, as pointed out above, it would have been obvious to use art known compounds in the liposomes of Hafez with the expectation of obtaining similar results since the principle is the same.

Applicant's arguments have been fully considered, but are not found to be persuasive. The examiner has already addressed applicant's arguments regarding Hafez. Applicant argues that Lishko teaches liposomal formulations of anionic and neutral lipids and that the combination suggested by Lishko would be unstable at a low pH. First of all, it should be pointed out that Lishko's liposomes contain DOPE, which is cationic, and therefore, the liposomes are not anionic. Secondly that the combinations suggested by Lishko would be unstable at a low pH is without any evidence and hence speculative.

4. Claims 1-3, 5-11 and 21-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Deshmukh et al (6,258,792).

Deshmukh while disclosing cationic cholesteryl derivatives teaches that while formulating liposomes these cationic cholesterol derivatives may be combined with DOTAP, anionic lipids such as phosphatidic acid and neutral lipids such as DOPE and

cholesterol. The biologically active agents include DNA, RNA or proteins. The liposome sizes are between 100 and 200 nm. (Abstract, col. 4, line 45 through col. 6, line 43 through col. 7, line 41; col. 7 line 46 through col. 8, line 50, col. 10, Examples). According to Deshmukh, the negatively charged lipid can be included so long as the net charge of the complexes formed is positive. It would have been obvious to one of ordinary skill in the art to prepare liposomes containing cationic lipid, anionic lipid and a neutral lipid based on the suggestion of Deshmukh et al with a reasonable expectation of success. The liposomes of Deshmukh et al would show the same isoelectric point since Deshmukh is suggestive of the same components and provide guidance for the preparation of liposomes with a reasonable expectation of success. Although Deshmukh does not teach liposomes having a overall negative charge at the physiological pH, since he teaches that a negatively charged lipid is included in the liposomes containing a cationic lipid as long as the resultant liposome is cationic, one of ordinary skill in the art would be motivated to vary the amounts of the cationic lipid and the anionic lipid as in instant claims to obtain a liposome with desired net positive or negative charge at physiological pH, depending upon the use of the liposome. Although Deshmukh does not teach instant cationic and anionic lipids such as HisChol and CHEMS respectively, it would have been obvious to use art known compounds in the liposomes of Deshmukh with the expectation of obtaining similar results.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that in order to facilitate loading and/or adherence of the negatively charged active substances into/onto the Deshmukh liposomes, the

Deshmukh liposomes must be cationic and consequently, Deshmukh limits itself actively to cationic lipid mixtures, even if anionic lipids are present. Furthermore, according to applicant Deshmukh cannot motivate the artisan to make liposomes that have a negative charge at physiological pH because it would make loading of the negatively charged active agents difficult or impossible. These arguments are not persuasive since on col. 7, lines 35-40 Deshmukh teaches that the negatively charged lipids are those comprising at least one lipid species having a net negative charge at or near physiological pH. Furthermore, Deshmukh refers to the charge of the complex as positive and not liposomes themselves. With regard to the difficulty or impossibility of loading of the negatively charged active agents at the physiological pH, the examiner points out that instant claims are not drawn to a method of loading. Furthermore, without any experimental evidence such comments are deemed to be speculative in nature.

5. Claims 5-11, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hafez cited above, in view of Deshmukh cited above.

The teachings of Hafez have been discussed above. What are lacking in Hafez are the teachings of the inclusion of a neutral lipid and the inclusion of an active agent. Deshmukh as pointed out above, teaches that a neutral lipid can be included in the liposomes containing a cationic lipid and anionic lipid. Deshmukh also teaches the use of these liposomes for the delivery of active agents such as DNA, RNA and proteins. It would have been obvious to one of ordinary skill in the art to include a neutral lipid or encapsulate active agents such as nucleic acids or proteins in the liposomes of Hafez with a reasonable expectation of success since Deshmukh teaches that neutral lipids

can be included in the liposomes and these liposomes can be used to encapsulate nucleic acids and proteins.

Applicant's arguments are not found to be persuasive. Applicant argues that the teachings of Hafez and Deshmukh cannot be properly combined because these references have different requirements that are mutually exclusive. According to applicant, Hafez teaches the creation of anionic liposomes at physiological pH and Deshmukh requires cationic liposomes. These arguments are not persuasive since the arguments regarding the nature of Deshmukh liposomes have been addressed above.

6. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Woodward Michael can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ S Kishore

Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK